SYNOPSIS

BV2012/05

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Title:	Clinical and immune modifying capacity of Broncho-Vaxom® tested by LPS-challenge in healthy volunteers. A randomised double-blind placebo-controlled trial
Short Title:	Broncho-Vaxom® in immune modifying capacity
Indication:	Experimental induced bronchitis in healthy volunteers
Phase:	2
Study Code:	BV2012/05
Study Director/ Co-ordinating Investigator:	Prof. Dr. Stefan Zielen
Study Centre:	The study was conducted at 1 site: Medaimun GmbH Kennedyallee 97a 60596 Frankfurt am Main Germany
Objectives:	To determine the magnitude of the effect of Broncho-Vaxom (BV) on a panel of immunological parameters in biological samples (blood/saliva and induced sputum), before and after 4 weeks of treatment and before and after a lipopolysaccharide (LPS) challenge, in order to allow identification of candidate immunological and pharmacodynamic biomarkers in both lung non-inflammatory and inflammatory status. <u>Primary Objective</u>: • To demonstrate that healthy volunteers treated with BV develop total antibody levels (i.e., total secretory immunoglobulin A (TsIgA) in saliva) after 4 weeks of treatment compared to placebo. <u>Planned Secondary Objectives</u>: To show reduction on 1 of the following inflammatory responses after an LPS-challenge: • Leukocytes, neutrophils, C-reactive protein (CRP), LPS-binding protein (LBP) levels in serum

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Objectives: (Cont'd)	• Neutrophilic inflammation and inflammatory cytokines in induced sputum • Bronchoconstriction (forced expiratory volume in 1 second (FEV_1) decrease) • Local symptoms: chest tightness, breathlessness, cough • Increases in the fraction of exhaled nitric oxide (FE_{NO}) • Systemic effects like increase of body temperature, chills and headache <u>Safety Objectives</u>: To analyse: • The vital signs • The physical examinations • The safety laboratory variables • The occurrence of adverse events (AEs) and serious adverse events (SAEs) <u>Planned Exploratory Objectives</u>: To analyse the evolution of specific immunological parameters in induced sputum, after 4 weeks of treatment and after the LPS-challenge.
Design:	Monocentre, randomised, double-blind, parallel, placebo-controlled study.
Treatment:	Subjects were allocated to 1 of the following treatments: BV 7 mg/day (BV-7), BV 21 mg/day (BV-21), or placebo. The randomisation allocation ratio was 1:1:1 using a blocked scheme. BV-7 arm (21 subjects): 1 capsule containing 7 mg of lyophilised bacterial extract out of 3 capsules (2 capsules with matched powder). BV-21 arm (21 subjects): 3 capsules containing 7 mg of lyophilised bacterial extract. Placebo arm (21 subjects): 3 capsules containing matched powder. Treatment period: 3 capsules/day, i.e., 7 or 21 mg/day, for 28 days. Mode of administration: oral route, to be taken with some fluid in the morning on an empty stomach.

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Inclusion Criteria:	1. Volunteer informed of the study procedures and medications and who had given his/her written informed consent. 2. Healthy male and female of any race. 3. Subject aged from 18 to 45 years.
Exclusion Criteria:	1. Subject who had received systemic or inhaled corticosteroids within 4 weeks before Visit 1. 2. Subject who had smoked on a regular basis within 2 years before Visit 1 or who had a smoking history >10 pack-years. 3. Subject with an active lung disease (e.g., asthma, chronic bronchitis, chronic obstructive pulmonary disease). 4. Subject who had suffered from a respiratory tract infection within 4 weeks preceding the study period. 5. Subject with predicted FEV_1 below 80% at Visit 1. 6. Subject with clinically significant uncontrolled systemic disease or a history of such disease (e.g., cancer, infection, haematological disease, renal, hepatic, coronary heart disease or other cardiovascular disease, endocrinology or gastrointestinal disease) within the previous 3 months. 7. Subject with clinically significant laboratory abnormalities at Visit 1. 8. Subject with a platelet count $\leq 130 \times 10^9$/L at Visit 1. 9. Subject with a result for the methacholine test below 0.1 mg at Visit 1. 10. Subject with skin prick test result >5 mm and a corresponding history of allergic asthma. 11. Subject with a clinically significant abnormal finding detected on electrocardiogram at Visit 1. 12. Subject with a history of food or drug related severe anaphylactoid or anaphylactic reaction(s). 13. Pregnant or nursing mothers. 14. Subject who was of child bearing potential and not protected by a reliable contraceptive method (oral, subcutaneous, mechanical, or surgical contraception). Any woman who became pregnant during the course of the study had to be discontinued; any female who started her menarche during the trial and was not, for whatever reason, protected by a medically approved contraception had to be withdrawn from the trial. 15. Subject with known hypersensitivity to any ingredients of BV.

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Exclusion Criteria: (Cont'd)	16. Subject who was considered potentially unreliable and subject who might not reliably attend study drug visits. 17. Subject with a history of drug or alcohol abuse. 18. Subject who was unable to perform spirometry and peak flow measurements or complete the subject's diary. 19. Subject who had participated in another clinical study within 3 months prior to Visit 1.
Primary and Secondary Endpoints:	<u>Primary Endpoints</u>: • Absolute and relative changes from baseline (Visit 2) in TsIgA level in saliva after 4 weeks of study treatment (Visit 3). <u>Planned Secondary Endpoints</u>: • Change in leukocytes, neutrophils, CRP and LBP levels in serum between morning pre LPS and 8 hours, 24 hours (Visit 5) or 48 hours (Visit 6) after the LPS-challenge. • Change in neutrophil count and cytokines (interleukin (IL)-5, IL-6, IL-8, IL-10, IL-12/23, IL-17, monocyte chemoattractant protein 1 (MCP-1), interferon gamma and tumour necrosis factor alpha (TNF-α)) in induced sputum between Visit 3 and Visit 5. (Note: Due to problems encountered with the quality of the biomarker data, the planned secondary efficacy analysis of the change in cytokine levels from Visit 3 to Visit 5 was replaced with an exploratory retrospective re-analysis.) • Bronchoconstriction during LPS-challenge (Visit 4), at Visit 5 and Visit 6 (maximum % FEV_1 decrease due to LPS-challenge). • Percentage of subjects presenting chest tightness/breathlessness/cough at Visit 4 due to the LPS-challenge (i.e., with a clinical symptoms score $\geq$1) and other reported symptoms; percentage of subjects presenting daytime/nocturnal symptoms (i.e., with a clinical symptoms score $\geq$1) after LPS-challenge (from subject diary), at Visit 5 and Visit 6; percentage of subjects having FE_{NO} $\geq$45 ppb after LPS-challenge, at Visit 5 and Visit 6. • Maximum increase in body temperature at Visit 4 between pre LPS and post LPS-challenge; occurrence of systemic effects reported as AEs during LPS-challenge (chills, headache).

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Primary and Secondary Endpoints: (Cont'd)	<u>Planned Exploratory Endpoints</u>: • Change in IL-6, IL-8, toll-like receptor (TLR)-4, forkhead box P3 (FoxP3), nucleotide-binding oligomerisation domain-containing protein 1 and 2 (NOD1/2), inducible T-cell costimulator (ICOS), and B-cell activating factor (BAFF) in induced sputum between Visit 2 and Visit 3 or Visit 5. Note: As part of the retrospective re-analysis of the biomarker data TLR-2 and TNF-α were also included in the exploratory analysis of candidate biomarkers. <u>Safety Endpoints:</u> • Vital signs • Physical examination • Safety laboratory variables • AEs and SAEs
Procedures:	Five- to eight-week study divided in 4 periods: • A 1- to 3-week screening period, between Visit 1 and Visit 2 (randomisation) • A 4-week double-blind treatment period, between Visit 2 and Visit 3 • An LPS-challenge the day following Visit 3, at Visit 4 • A 2-day post LPS-challenge period, Visit 5 and Visit 6 being respectively performed 24 h and 48 h after the LPS-challenge
Sample Size:	Sixty subjects were planned (20 subjects per treatment arm), and the number was based on a Jonckheere-Terpstra test performed with a power of 80%, taking into account odds ratios above 3 between both experimental treatment arms and placebo arm. Seventy-three subjects were screened of which 63 were randomised.
Statistical Methods:	Although only 1 analysis and Clinical Study Report (CSR) was planned, problems with the quality of the cytometric bead array (CBA) and quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) data were identified a posteriori. • qRT-PCR data were incorrectly derived. In particular, the Δ cycle threshold (Δ Ct) data were all inverted, resulting in opposite final results (i.e., level decreases instead of increases).

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Statistical Methods:	• The quantification flags of CBA protein expression data, indicating whether the measure was below the limit of quantification (BLOQ), in range, or above the upper limit of quantification (ULOQ), were incorrectly taken into account. • Overall, no problems were identified in the primary endpoint variable (TsIgA). As a result of these problems, a retrospective exploratory re-analysis of the CBA and qRT-PCR data was conducted with corrected data after appropriate quality controls and updates. An additional supportive exploratory analysis of the primary endpoint variable (TsIgA) was also included. All of the re-analyses are considered as exploratory retrospective analyses, as the statistical approaches used were not planned in the original statistical analysis plan (SAP). A revised SAP was prepared for the purpose of these exploratory retrospective analyses. For the planned primary efficacy endpoint, the null hypothesis (H_0) tested was: $\theta_0 = \theta_7 = \theta_{21}$ where θ_0 stands for the median of the placebo group, θ_7 stands for the median of the BV-7 group and θ_{21} stands for the median of the BV-21 group. The alternative hypothesis (H_1) was: $\theta_0 \leq \theta_7 \leq \theta_{21}$ (with at least 1 of the inequalities being strict). Analysis was performed using the Jonckheere-Terpstra test. Furthermore, post-hoc Wilcoxon-Mann-Whitney tests for pairwise group comparisons (placebo versus BV-21, placebo versus BV-7 and BV-7 versus BV-21) were added in case of significant differences between the treatment groups. These tests were 2-sided with a significance level adjusted according to the Bonferroni-Holm closed test procedure. A sensitivity analysis was also performed using the Kruskal-Wallis test (no a priori ordering) instead of the Jonckheere-Terpstra test. For the originally planned analyses, continuous secondary efficacy endpoints were compared by the Jonckheere-Terpstra test and no post-hoc tests had to be added in case of significant differences between the treatment groups. Categorical secondary efficacy endpoints were compared between the treatment groups with chi-square tests (or Fisher exact tests if expected cell counts would be less than 5). All tests were 2-sided with a significance level of α=5%. For the retrospective exploratory re-analysis (performed on the full analysis set (FAS)), the biomarker data (qRT-PCR gene expressions and CBA protein expressions) and TsIgA concentrations were read from raw laboratory data files.

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Statistical Methods:	Their contents were standardised and reconciled with previously aggregated data in the clinical database in order to identify and solve all discrepancies. Quality control was then performed on each biomarker dataset. In particular, the randomisation schema and the batch effects were controlled, as well as the BLOQ and ULOQ thresholds. TsIgA and biomarker qRT-PCR and CBA data were log-transformed prior to statistical analysis in order to approach a normal distribution and hence allow parametric methods. The changes of biomarker expression after 4 weeks of treatment and during the LPS-challenge were assessed separately, adjusting for respective baseline values and additional covariates. An analysis of covariance (ANCOVA) was used to assess the significance of the treatment arm term in tested models. Biomarker expression changes associated with treatment with a p-value ≤ 0.05 were reported. No imputation of missing data was carried out. Full details of the statistical methods in the re-analysis are provided in the Exploratory Biomarker SAP. The FAS was used for analysis of all efficacy endpoints, with additional supportive analyses carried out on the per-protocol set (PPS) for the primary endpoint.
Results:	A total of 73 subjects were screened from 13 September 2012, to 7 November 2012, of whom 63 (86.3%) were randomised into the study; 21 subjects in the placebo treatment arm, 21 subjects in the BV-7 arm and 21 subjects in the BV-21 arm. All subjects received at least 1 dose of study medication and were thus included in the safety set (SS), as well as in the FAS. A total of 3 subjects were excluded from the PPS analysis, 1 subject in each treatment group. Populations of analysis were as follows: • SS = FAS = 63 subjects (21 in each treatment group). • PPS = 60 subjects (20 in each treatment group). **Demographic, Baseline, and Other Relevant Characteristics** • As expected for this population of healthy volunteers, the BV and placebo treatment groups were comparable with regard to baseline and demographic characteristics. Subjects were predominantly non-smokers (95.2%), and the mean (SD) age was 24.9 (4.1) years old (range, 18 to 38).

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Results: (Cont'd)	• Allergic disorders were more common in the BV groups, with known allergic rhino conjunctivitis reported for 7 subjects in the BV groups combined versus 0 in the placebo group, and a history of atopic dermatitis reported for 4 subjects in the BV groups combined, compared to 0 subjects in the placebo group. • The methacholine test result was negative at baseline for 11 (52.4%) subjects in each of the BV treatment groups compared to 15 (71.4%) in the placebo group. Spirometric lung function assessments were similar across the 3 treatment groups. The mean (SD) FE_{NO} was slightly increased at baseline in the BV-21 group compared with the BV-7 and placebo groups (22.07 (25.5) ppb, 17.3 (9.4) ppb, and 16.2 (14.5) ppb, respectively). • Concomitant medications were comparable between the 3 treatment groups. • Sixty subjects (95.2%, 20 in each treatment group) completed the study as per protocol, and none dropped out during the course of the study. • Overall, the mean (SD) duration of the study treatment was 28.0 (0.3) days, almost identical to the theoretical time of 28 days, ranging from 27 to 29 days, with no difference between the 3 treatment groups. The compliance was good (>80% of capsules taken) for all subjects and similar between treatment groups. **Primary Endpoint: Change in TsIgA Levels After 4 Weeks of Study Treatment** • The primary efficacy analysis did not demonstrate a statistically significant difference among treatment groups for the absolute or relative change in TsIgA levels in saliva after 4 weeks of study treatment. However, a trend toward a dose-dependent increase in median TsIgA levels in the BV treatment groups was observed (i.e., median relative change of +5.59% versus 0.00% versus -3.07% in the BV-21, BV-7, and placebo groups, respectively). These results were confirmed in the exploratory retrospective re-analysis using ANCOVA. Interpretation of data was, however, limited by high inter-subject variability in data observed both at Visit 2 and Visit 3. Although there was no statistically significant difference across treatment groups at baseline (i.e., Visit 2), the observed median TsIgA level was higher in the BV-21 group (4.3 mg/dL) than in the BV-7 (4.0 mg/dL) and placebo (3.6 mg/dL) groups.

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Results: (Cont'd)	• Mean neutrophils in induced sputum increased comparably across treatment groups following LPS-challenge, with no statistically significant differences among groups for the change from Visit 3 to Visit 5. • An exploratory retrospective analysis of the change in cytokine protein levels in induced sputum 24 hours post LPS-challenge (Visit 3 to Visit 5) demonstrated no statistically significant difference among treatment groups for IL-6, IL-8, IL-17, IL-12/23, and MCP-1. IL-6, IL-8, and MCP-1 were statistically significantly up-regulated following LPS-challenge, independent of treatment arm, whereas there were no statistically significant changes in the levels of IL-17 or IL-12/23. Levels of TNF-α, IL-5, IL-10 and IFN-γ were mostly BLOQ at both time points (Visit 3 and Visit 5) and therefore could not be included in the analysis. • Bronchoconstriction, as measured by FEV_1, remained relatively constant post LPS-challenge, with no statistically significant differences among treatment groups. The proportion of subjects presenting at least 1 local symptom (like chest tightness, cough and breathlessness), was statistically significantly higher in the placebo group (28.6%) at 30 minutes post LPS-challenge compared to either the BV-7 group (0%) or the BV-21 group (9.5%) (p=0.022). However, at later time points, the differences among treatment groups were not statistically significant. There was no statistical difference among treatment groups in the proportion of subjects reporting daytime/nocturnal symptoms at Visit 5 or Visit 6. For FE_{NO}, there was a trend toward greater increases in the placebo group, compared to BV-7 and BV-21, at each of the measured time points post LPS-challenge, although the differences among treatment groups were not statistically significant. • Body temperature increased steadily in each of the 3 treatment groups over the 9 hours measured post LPS-challenge, with no statistically significant difference among groups except for the 7-hour time point, at which the mean (SD) increase in temperature was slightly lower in the BV-21 group (0.4 (0.4)°C) compared to the BV-7 (0.8 (0.6)°C) and placebo group (0.6 (0.5)°C) (p=0.033). During the LPS-challenge, AEs were recorded for 8 (12.7%) subjects, with comparable proportions in the 3 treatment groups.

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Results:
(Cont'd)

Exploratory Endpoints

Change in Cytokine Protein Levels in Induced Sputum After 4 Weeks of Study Treatment

- In an exploratory retrospective analysis of the change in cytokine protein levels from Visit 2 to Visit 3, a statistically significant difference among treatment groups was found for IL-8 (p=0.025) and MCP-1 (p=0.032), whereas there were no statistically significant differences among treatment groups for IL-6, IL-17, and IL-12/23. For IL-8, a dose-dependent down-regulation was observed in the BV treatment groups. However, the statistically significant difference across treatment arms for IL-8 appeared to be driven by lower baseline concentrations at Visit 2 in the placebo arm, and there were no statistically significant differences for the change in IL-8 levels from Visit 2 to Visit 3 in either of the 2 BV treatment arms. For MCP-1, the statistically significant difference across treatment arms appeared to be driven by apparent up-regulation in the BV-7 treatment arm, and there were no statistically significant differences from Visit 2 to Visit 3 in any of the 3 treatment arms. Furthermore, IL-6, IL-8, and IL-12/23 appeared to be up-regulated in the placebo arm; however, the increases in levels from Visit 2 to Visit 3 were statistically significant for IL-8 (p=0.012) only. The only statistically significant changes in the BV treatment groups were overall mean (SD) fold increases of 1.35 (0.47) for IL-6 in the BV-7 group and 1.17 (0.32) for IL-12/23 in the BV-21 group.

Change in Gene Expression of Candidate Biomarkers After 4 Weeks of Study Treatment and Post LPS-Challenge

- Differences among treatment groups for the change in gene expression from Visit 2 to Visit 3 were found to be statistically significant for FoxP3, which was dose-dependently up-regulated after 4 weeks of treatment with BV as compared to placebo (p=0.035). No statistically significant between-group differences were observed for BAFF, ICOS, IL-6, IL-8, NOD1, NOD2, TNF-α, TLR-2, and TLR-4, although a dose-dependent trend for an up-regulation of gene expression was observed in the BV groups for ICOS, IL-8 and TLR-4, as well as an up-regulation of BAFF gene expression in the BV-21 group as compared to the placebo or BV-7 treatment groups. A trend for down-regulation of IL-6 was observed in the BV treatment groups relative to placebo.

With the exception of IL-6 and TNF-α, which showed a trend toward decreased expression, most cytokines were up-regulated upon LPS-challenge, although between-group differences were not statistically significant for the majority of cytokines.

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Results: (Cont'd)	Dose-dependent up-regulation of both BAFF and ICOS were observed, with borderline significant up-regulation of IL-8; however, there was considerable inter-individual variability for IL-8. Higher up-regulation of TLR-2 was observed in the BV-7 group as compared to the placebo or BV-21 treatment groups. **Safety** <u>Adverse Events</u> Of the 63 included subjects, 29 (46.0%) subjects presented 68 AEs during the study: 9 (42.9%) subjects in the BV-21 group, 11 (52.4%) subjects in the BV-7 group and 9 (42.9%) subjects in the placebo group experienced at least 1 AE. The most frequently reported AEs by system organ class during the study involved Nervous System Disorders (22.2%); Respiratory, Thoracic and Mediastinal Disorders (14.3%); General Disorders and Administration Site Conditions (11.1%); and Infections and Infestations (9.5%). Headache was the most frequently (≥5%) reported AE, with a similar incidence between the 3 treatment groups (approximately 20%). There was a higher incidence of oropharyngeal pain for subjects who received BV-21 (23.8%) compared with subjects who received BV-7 (0.0%) or placebo (4.8%). Thirteen treatment-related AEs occurred in 9 (14.3%) subjects: i.e., 4 subjects in the BV-21 group (6 AEs involved), 3 subjects in the BV-7 group (5 AEs involved), and 2 subjects in the placebo group (2 AEs involved: headache and cough). Headache was reported as a treatment-related AE with equal incidence across all 3 treatment groups (i.e., 1 subject per group). Treatment-related AEs which were reported in the BV groups but not in the placebo group were as follows: oropharyngeal pain (2 subjects), throat irritation, fatigue, and abdominal pain upper (1 subject each) in the BV-21 group; and feeling cold, constipation, alanine aminotransferase increased, and aspartate aminotransferase increased (1 subject each) in the BV-7 group. Treatment-related cough was reported for 1 subject in the placebo group compared to no subjects in the BV groups. No severe treatment-related AEs nor AEs leading to permanent discontinuation were reported during the study. No deaths nor other SAEs occurred during the course of the study. During the LPS-challenge, AEs were recorded for 8 subjects (12.7%), with comparable proportions in the 3 treatment groups.

Name of Company:	OM Pharma SA
Name of Finished Product:	Broncho-Vaxom® 7 mg
Name of Active Ingredient(s):	Bacterial lysates of Haemophilus influenzae; Streptococcus pneumoniae; Klebsiella pneumoniae ssp. pneumoniae and Klebsiella pneumoniae ssp. ozaenae; Staphylococcus aureus; Streptococcus pyogenes and Streptococcus sanguinis (viridans); and Moraxella (Branhamella) catarrhalis

Results: (Cont'd)	<u>Vital Signs, Physical Findings and Other Observations Related to Safety</u> Vital signs (i.e., heart rate and blood pressure) showed no clinically relevant changes during study, and there were no remarkable physical exam or electrocardiogram findings. There were no significant differences in laboratory parameters between the 3 treatment groups.
Conclusion:	Overall, the study failed to demonstrate a statistically significant effect of BV to enhance the clinical and immune mucosal barrier properties in healthy volunteers, although non-statistically significant trends for a dose-dependent up-regulation of some biomarkers were observed. The results for the primary endpoint did not demonstrate a statistically significant change in TsIgA in saliva in healthy volunteers treated with BV for a 28-day period, although a dose-dependent trend for an increase of median TsIgA levels in saliva was observed in the BV treatment groups relative to placebo. Similarly, results for the secondary endpoints measuring inflammatory parameters post LPS-challenge were generally similar across the BV and placebo treatment groups. Overall, 2 candidate pharmacodynamic biomarkers in sputum were identified from the retrospective exploratory analyses: FoxP3 gene expression and IL-8 protein expression following 4 weeks of treatment with BV. However, the inter-subject variability and the significant differences at baseline observed between treatment arms need to be better understood before reaching definite conclusions. Noteworthy limitations of the study include the following: high inter-individual variability (particularly for TsIgA and cytokine levels); differences observed in baseline characteristics between the treatment groups with respect to a higher occurrence of known allergies in the BV treatment groups; different baseline protein and/or gene expression levels of cytokines and biomarkers in the placebo group compared to the BV groups; and, the small sample size. In terms of safety, BV, at both doses, 21 mg/day and 7 mg/day, proved to be safe and well tolerated when given for a 28-day treatment period, which is in line with previous experience with the product.